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KIRKPATRICK & LOCKHART NICHOLSON GRAHAM LLP STATE STREET FINANCIAL CENTER ONE LINCOLN STREET BOSTON, MA 02111-2950			JUNG, UNSU	
			ART UNIT	PAPER NUMBER
			1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,740	CAUWENBERGHS ET AL.	
	Examiner	Art Unit	
	Unsu Jung	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 January 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 31-41 and 46-61 is/are pending in the application.
- 4a) Of the above claim(s) 46 and 47 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31-41 and 48-61 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 January 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>10/24/05 & 1/18/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicants' amendments to the specification in the reply filed on January 18, 2006 are acknowledged and entered.
2. Applicants' amendments to add new claims 60 and 61 and amend claims 31, 32, and 57 in the reply filed on January 18, 2006 are acknowledged.
3. Claims 31-41 and 46-61 are pending.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on October 24, 2005 has been considered by the examiner. However, the IDS submitted on October 24, 2005 contains the following errors:
 - Falkenber et al. (Ref. No. C8): the journal name should include "J." preceding "Immunol. Methods"
 - Merrifield (Ref. No. C29): the ending page number should be corrected to "2154"
 - Wittmann-Liebold et al. (Ref. No. C50): the ending page number should be corrected to "107"

Objections Withdrawn

5. Applicant's arguments, see p9, filed January 18, 2006, with respect to the objection of the drawings have been fully considered and are persuasive. The objection of the drawings has been withdrawn in light of the amended drawings Fig. 1, Fig. 3, and Fig. 4 in the reply filed on January 18, 2006.

6. Applicant's arguments, see p10, filed January 18, 2006, with respect to the objection of claims have been fully considered and are persuasive. The objection of claims 32, 39, 48, and 49 has been withdrawn in light of the amended claims 32 and 39 in the reply filed on January 18, 2006.

Rejections Withdrawn

7. Applicant's arguments, see pp10-11, filed January 18, 2006, with respect to the rejection under 35 U.S.C. 112, first paragraph have been fully considered and are persuasive. The rejection of claim 53 under 35 U.S.C. 112, first paragraph has been withdrawn in light of the specification.

8. Applicant's arguments, see p11, filed January 18, 2006, with respect to the rejection under 35 U.S.C. 112, second paragraph have been fully considered and are persuasive. The rejection of claims 31-41 and 48-59 under 35 U.S.C. 112, second paragraph has been withdrawn in light of the amended claims 31 and 32.

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9. Applicant's arguments, see pp11-12, filed January 18, 2006, with respect to the rejection under 35 U.S.C. 103(a) as being unpatentable over Favaloro et al. (*Pathology*, 1993, Vol. 25, pp152-158) in view of Hoylaerts et al. (*Biochem. J.*, 1995, Vol. 386, pp453-463) have been fully considered and are persuasive. The rejection of claims 31-33, 35, 37-41, 48, and 49 under 35 U.S.C. 103(a) as being unpatentable over Favaloro et al. in view of Hoylaerts et al. has been withdrawn in light of applicants' argument in the reply filed on January 18, 2006.

10. Applicant's arguments, see p13, filed January 18, 2006, with respect to the rejection under 35 U.S.C. 103(a) as being unpatentable over Favaloro et al. (*Pathology*, 1993, Vol. 25, pp152-158) in view of Hoylaerts et al. (*Biochem. J.*, 1995, Vol. 386, pp453-463), and further in view of Handin (U.S. Patent No. 5,321,127, Filed Mar. 18, 1991) have been fully considered and are persuasive. The rejection of claims 34, 36, 50-53, and 56-59 under 35 U.S.C. 103(a) as being unpatentable over Favaloro et al. in view of Hoylaerts et al. and further in view of Handin has been withdrawn in light of applicants' argument in the reply filed on January 18, 2006.

11. Applicant's arguments, see pp13-14, filed January 18, 2006, with respect to the rejection under 35 U.S.C. 103(a) as being unpatentable over Favaloro et al. (*Pathology*, 1993, Vol. 25, pp152-158) in view of Hoylaerts et al. (*Biochem. J.*, 1995, Vol. 386, pp453-463) and Handin (U.S. Patent No. 5,321,127, Filed Mar. 18, 1991), and further in view of Elings et al. (U.S. Patent No. 4,537,861, Filed Feb. 3, 1983) have been fully

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considered and are persuasive. The rejection of claim 54 under 35 U.S.C. 103(a) as being unpatentable over Favaloro et al. in view of Hoylaerts et al. and Handin, and further in view of Elings et al. has been withdrawn in light of applicants' argument in the reply filed on January 18, 2006.

Specification

12. The use of the trademark SEPHAROSE® (p18, line 27) have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The trademark, SEPHAROSE® (p18, line 27), should be capitalized.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 31-41 and 48-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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15. Claim 31 recites the limitation "the amount" in step (b). There is insufficient antecedent basis for this limitation in the claim.

16. Claim 31 recites the limitation "the ratio" in step (c). There is insufficient antecedent basis for this limitation in the claim.

17. In claim 31, the term "vWF-antigen" in step (c) is vague and indefinite. It is not clear whether or not the term "vWF-antigen" is referring to the "vWF-antigen" in step (b).

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

19. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

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20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 31, 40, 41, 48-50, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Favalaro et al. (*Pathology*, 1993, Vol. 25, pp152-158) in view of Christophe et al. (*Blood*, 1994, Vol. 83, pp3553-3561), and Handin (U.S. Patent No. 5,321,127, June 14, 1994).

Favalaro et al. teaches a method for detecting von-Willebrand disease (vWD) comprising the steps of (Abstract):

- a) detecting von-Willebrand factor (vWF) activity in a sample (p153, right column, *Collagen binding assay for vWF*);
- b) determining the amount of vWF-antigen in the sample (p153, left column, *ELISA assay for vWF:Ag*);
- c) determining the ratio between vWF-activity and vWF-antigen for the sample (Abstract);

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- d) comparing the ratio obtained under c) to a range of ratios established as normal range (p154, Table 1);
- e) detecting vWD based on the comparison result obtained under step (d) (Abstract).

Favaloro et al. further teaches that type 1 vWD patients suffer from a quantitative reduction in all vWF multimers present, with concurrently decreased levels of vWF:Ag and ristocetin cofactor activity (p152, right column, *Introduction*, 2nd paragraph).

Alternatively, type 2 vWD is characterized by qualitative abnormalities of vWF multimers (p152, right column, *Introduction*, 2nd paragraph). Classification of the patient's vWD is important not only because the biological activity of vWF is related to its multimeric profile, but also since subsequent clinical management of such patients may differ substantially on this basis (p152-3, *Introduction*, 2nd paragraph). However, Favaloro et al. fails to teach a detection step of a) uses a soluble form or a portion of glycoprotein 1b(α) (GP1b(α)) and ristocetin or a functionally equivalent substance.

Christophe et al. teaches that type 2B vWD is characterized by the absence of the highest molecular weight multimers in plasma and the capacity to interact with GP1b in the presence of concentration of ristocetin or botrocetin too low to promote the binding of normal vWF (p3553, *Introduction*, right column, lines 1-6). This increased binding capacity for GP1b allows the spontaneous binding of the largest vWF multimers to this receptor, leading to their clearance from plasma and intermittent thrombocytopenia (p3553, *Introduction*, right column, lines 6-15). Christophe et al. further teaches ristocetin induced platelet aggregation analysis (RIPA), which measures

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aggregation (agglutination) of platelets under low concentrations of ristocetin (p3554, right column, *Binding of plasma vWF and rvWF to platelet GP1b*). However, Christophe et al. fails to teach an RIPA assay further including the use of a soluble form or a portion of GP1b(α).

Handin teaches that GP1b receptor subunit GP1b(α) contains the receptor's vWF binding site (column 2, lines 39-51). Specifically, glycoalcin, which contains the majority of the extracellular portion of GP1b(α), can inhibit ristocetin-dependent binding of vWF (column 2, lines 51-68). Handin further teaches a platelet aggregation assay for measuring vWF activity using ristocetin and recombinant (soluble) GP1b(α) containing vWF interaction site (column 3, lines 35-39 and column 20, lines 60-68).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute vWF activity detection method of Favaloro et al. with a method detecting ristocetin-mediated vWF binding using soluble form of GP1b(α) as taught by Handin in order to specifically detect patient's ristocetin-dependent vWF binding activity to platelets to determine mutant vWF associated with type 2 vWD, which has increased affinity for platelet GP1b at low ristocetin or botrocetin concentrations as taught by Christophe et al. One of ordinary skill in the art would readily recognize that the use of Handin's soluble form of GP1b(α) would be advantageous in the platelet aggregation assay to detect specific GP1b-vWF binding activity.

With respect to claim 40, Favaloro et al. (p153, right column, *Ristocetin cofactor assay*) and Handin (column 15, line 54-column 16, line 19 and column 20, lines 61-68)

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teaches a method of detecting vWF activity under step a) using a homogeneous agglutination assay.

With respect to claim 41, Favaloro et al. teaches a method, wherein the sample is obtained from plasma of a patient (p152, right column, *Introduction*, lines 4-9).

With respect to claims 48 and 49, Favaloro et al. teaches a method, wherein detecting vWD under step e) comprises discriminating between type 1 and type 2 vWD (p153, left column, *Introduction*, lines 17-23).

With respect to claim 50, Handin teaches a method of obtaining a recombinant human platelet GP1b(α) receptor fragments containing the vWF binding site (column 3, lines 5-11).

With respect to claim 60, Handin teaches a soluble form or a portion of GP1b(α) containing an N-terminal domain of GP1b(α) (column 2, line-column 3, line 2).

22. Claims 31-39, 41, 48-53, and 56-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Favaloro et al. (*Pathology*, 1993, Vol. 25, pp152-158) in view of Christophe et al. (*Blood*, 1994, Vol. 83, pp3553-3561), Hoylaerts et al. (*Biochem. J.*, 1995, Vol. 386, pp453-463), and Handin (U.S. Patent No. 5,321,127, June 14, 1994).

Favaloro et al. teaches a method for detecting von-Willebrand disease (vWD) comprising the steps of (Abstract):

- a) detecting von-Willebrand factor (vWF) activity in a sample (p153, right column, *Collagen binding assay for vWF*);

- b) determining the amount of vWF-antigen in the sample (p153, left column, *ELISA assay for vWF:Ag*);
- c) determining the ratio between vWF-activity and vWF-antigen for the sample (Abstract);
- d) comparing the ratio obtained under c) to a range of ratios established as normal range (p154, Table 1);
- e) detecting vWD based on the comparison result obtained under step (d) (Abstract).

Favaloro et al. further teaches that type I vWD patients suffer from a quantitative reduction in all vWF multimers present, with concurrently decreased levels of vWF:Ag and ristocetin cofactor activity (p152, right column, *Introduction*, 2nd paragraph).

Alternatively, type II vWD is characterized by qualitative abnormalities of vWF multimers (p152, right column, *Introduction*, 2nd paragraph). Classification of the patient's vWD is important not only because the biological activity of vWF is related to its multimeric profile, but also since subsequent clinical management of such patients may differ substantially on this basis (p152-3, *Introduction*, 2nd paragraph). However, Favaloro et al. fails to teach a detection step of a) uses a soluble form or a portion of glycoprotein 1b(α) (GP1b(α)) and ristocetin or a functionally equivalent substance.

Christophe et al. teaches that type 2B vWD is characterized by the absence of the highest molecular weight multimers in plasma and the capacity to interact with GP1b in the presence of concentration of ristocetin or botrocetin too low to promote the binding of normal vWF (p3553, *Introduction*, right column, lines 1-6). This increased

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binding capacity for GP1b allows the spontaneous binding of the largest vWF multimers to this receptor, leading to their clearance from plasma and intermittent thrombocytopenia (p3553, *Introduction*, right column, lines 6-15). Christophe et al. further teaches ristocetin induced platelet aggregation analysis (RIPA), which measures aggregation (agglutination) of platelets under low concentrations of ristocetin (p3554, right column, *Binding of plasma vWF and rvWF to platelet GP1b*). However, Christophe et al. fails to teach an RIPA assay further including the use of a soluble form or a portion of GP1b(α).

Hoylaerts et al. teaches a method of detecting vWF activity in a sample (human plasma) using a soluble form or a portion of glycoprotein 1b (GP1b) and ristocetin (p454, *Purification of GPIb*, *Purification of vWF*, and *Studies of Interaction between vWF and GPIb*). Hoylaerts et al. teaches that the ristocetin-mediated vWF binding to immobilized GPIb is a reversible event (p457, right column, *Specificity of ristocetin-mediated vWF binding to GPIb*, lines 1-3). Therefore, coated GPIb is considered suitable for the study of ristocetin-dependent interactions between GPIb and vWF using an enzyme-linked immunoabsorbent assays (ELISA) format assay (p457, right column, *Specificity of ristocetin-mediated vWF binding to GPIb*, lines 4-6). To study this binding quantitatively, pure-GPIb-coated microtiter plates potentially offered an advantage over agglutination studies with formalin fixed platelets, in which ristocetin-mediated interactions with other platelet proteins participate (p457, right column, *Specificity of ristocetin-mediated vWF binding to GPIb*, lines 6-10). Hoylaerts et al. further teaches that in order to avoid-non-specific ristocetin-dependent molecular interactions, isolated

GP1b was used instead of whole platelets (p462, left column, Discussion, 3rd paragraph). However, Hoylaerts et al. fails to teach a use soluble GP1b(α) in the vWF-binding activity.

Handin teaches glyocalicin, which contains the majority of the extracellular portion of GP1b(α) and can inhibit ristocetin-dependent binding of vWF (column 2, lines 51-68). Handin further teaches a method of obtaining human platelet GP1b(α) receptor fragments containing the vWF binding site (column 3, lines 5-11) and antibody against the GP1b(α) receptor fragment. Handin teaches that the antibodies and substantially purified antigen can be incorporated in a kit form such as ELISA (column 11, line 61-column 12, line 7), which involves immobilized antibodies either covalently or physically bound to a solid phase immunoabsorbent such as glass, polystyrene, polypropylene, dextran, nylon, and other materials in the form of tubes, beads, and microtiter plates (column 12, lines 47-61). Those skill in the art will appreciate that antibodies will be useful in other variations and forms of assays, which are presently known or may be developed in the future (column 12, lines 12-17).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute vWF activity detection method of Favaloro et al. with a method detecting ristocetin-mediated vWF binding to immobilized GP1b as taught by Hoylaerts et al. in order to quantitatively detect patient's vWF binding activity to determine mutant vWF associated with type 2 vWD, which has increased affinity for platelet GP1b at low ristocetin and botrocetin concentrations as taught by Christophe et al. The method of Hoylaerts et al. has an advantage over RIPA agglutination studies of

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Christophe et al. using formalin fixed platelets, in which ristocetin-mediated interactions with other platelet proteins participate, since the method of Hoylaerts et al. excludes the possibility of non-specific interaction of other platelet-derived proteins by using an isolated form of GP1b. In addition, it would have been obvious to one of ordinary skill in the art at the time of the invention to use a specific fragment of GP1b (extracellular fragment of GP1b(α)) as taught by Handin (soluble form) in the ELISA method of Hoylaerts et al. as the fragment of Handin contains ristocetin-dependent vWF binding site. One of ordinary skill in the art would recognize that the use of extracellular fragment of GP1b(α), which contains ristocetin-dependent vWF binding site, would be advantageous over the receptor complex GP1b of Hoylaerts et al., which contains components (such as GPIX) that are not involved in specific binding activity of vWF and increase likelihood of non-specific binding of vWF compared to assay Hoylaerts et al. assay using extracellular fragment of GP1b(α).

With respect to claim 32, Hoylaerts et al. teaches a method of detecting vWF activity comprising detecting a formation of a complex of vWF and GP1b(α) (p p454, *Purification of GPIb, Purification of wWF, and Studies of Interaction between vWF and GPIb*).

With respect to claim 33, Hoylaerts et al. teaches a method of detecting vWF activity, wherein the method of detecting vWF activity, wherein is bound to a solid support (p454, left column, *Studies of Interaction between vWF and GPIb*, lines 2-5).

With respect to claims 34 and 36, Handin teaches a method of immobilizing anti-GP1b(α) antibody to a solid support (column 12, lines 47-61), which can be used in the

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detection assay for determining vWF activity, wherein a complex of vWF and GP1b(α) is formed as taught by Hoylaerts et al. (p454, *Studies of interaction between vWF and GPIb*).

With respect to claim 35, Hoylaerts et al. teaches a method of detecting vWF activity, wherein the complex of vWF and GP1b(α) is bound to a solid support (p454, *Purification of GPIb, Purification of vWF, and Studies of Interaction between vWF and GPIb*).

With respect to claim 37, Hoylaerts et al. teaches a method of detecting vWF activity, wherein the detecting vWF activity under step a) comprises using an anti-vWF antibody (p454, right column, lines 30-33).

With respect to claims 38 and 39, Hoylaerts et al. teaches a method of detecting vWF activity under step a) comprising an ELISA (p454, right column, lines 30-33).

With respect to claim 41, Favaloro et al. teaches a method, wherein the sample is obtained from plasma of a patient (p152, right column, *Introduction*, lines 4-9).

With respect to claims 48 and 49, Favaloro et al. teaches a method, wherein detecting vWD under step e) comprises discriminating between type 1 and type 2 vWD (p153, left column, *Introduction*, lines 17-23).

With respect to claim 50, Handin teaches a method of obtaining a recombinant human platelet GP1b(α) receptor fragments containing the vWF binding site (column 3, lines 5-11).

With respect to claim 51, Handin teaches that the antibody against the GP1b(α) receptor fragment is a monoclonal antibody (column 9, lines 43-44).

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With respect to claim 52, Hoylaerts et al. teaches a method of detecting vWF activity, wherein the detecting vWF activity under step a) comprises using an anti-vWF antibody, which is detectably labeled (p454, right column, lines 30-33).

With respect to claim 53, Handin teaches a solid support, which is selected from a group consisting of glass, polystyrene, polypropylene, dextran, and nylon (column 12, lines 47-61).

With respect to claim 56, Hoylaerts et al. teaches a method of detecting vWF activity, wherein the sample is diluted (p454, left column, *Studies of interaction between vWF and GPIb*, lines 5-7).

With respect to claims 57-59, Handin teaches a method of immobilizing anti-GP1b(α) antibody to a solid support (column 12, lines 47-61), which can be used in the detection assay for determining vWF activity, wherein a complex of vWF and GP1b(α) is formed as taught by Hoylaerts et al. (p454, *Studies of interaction between vWF and GPIb*).

With respect to claim 60, Handin teaches a soluble form or a portion of GP1b(α) containing an N-terminal domain of GP1b(α) (column 2, line-column 3, line 2).

23. Claims 54 is rejected under 35 U.S.C. 103(a) as being unpatentable over Favaloro et al. (*Pathology*, 1993, Vol. 25, pp152-158) in view of Christophe et al. (*Blood*, 1994, Vol. 83, pp3553-3561), Hoylaerts et al. (*Biochem. J.*, 1995, Vol. 386, pp453-463), and Handin (U.S. Patent No. 5,321,127, June 14, 1994) as applied to claim 53 above, and further in view of Batz et al. (U.S. Patent No. 4,415,700, Nov. 15, 1983).

Favaloro et al. in view of Christophe et al., Hoylaerts et al. and Handin teaches a method for detecting vWD as discussed above. However, Favaloro et al. in view of Christophe et al., Hoylaerts et al. and Handin fails to teach a method, wherein the solid support comprises a latex bead.

Batz et al. teaches hydrophilic latex particles (beads), which can be used to covalently bind biologically and immunologically active substances either directly or via a coupling agent (Abstract). The hydrophilic latex particles of Batz et al. do not impair the structure and activity of the biologically and immunologically active substances, are stable under centrifuging conditions, can subsequently be resuspended again easily (column 2, line 59-column 3, line 2), and are especially useful for use in RIA, EIA, ELISA tests (column 5, lines 16-20).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to use hydrophilic latex particles (beads) as a solid support having biologically and immunologically active substances as taught by Batz et al. in the ELISA test of Favaloro et al. in view of Christophe et al., Hoylaerts et al. and Handin for measuring binding activity of vWF as the hydrophilic latex particles provide a solid support especially useful for ELISA tests without impairing the structure and activity biologically and immunologically active substances bound on the particles. Furthermore, the hydrophilic latex particles are especially useful in ELISA tests, which requires various incubation and washing steps of reagents and samples, since the particles are stable under centrifuging conditions and can subsequently be resuspended again easily.

24. Claims 55 is rejected under 35 U.S.C. 103(a) as being unpatentable over Favalaro et al. (*Pathology*, 1993, Vol. 25, pp152-158) in view of Christophe et al. (*Blood*, 1994, Vol. 83, pp3553-3561), and Handin (U.S. Patent No. 5,321,127, June 14, 1994) as applied to claim 40 above, and further in view of Solen et al. (U.S. Patent No. 6,043,871, Filed Mar. 3, 1997).

Favalaro et al. in view of Christophe et al. and Handin teaches a method for detecting vWD as discussed above. However, Favalaro et al. in view of Christophe et al. and Handin fails to teach a method, wherein the agglutination is measured by light scattering.

Solen et al. teaches a method of measuring platelet aggregation in whole blood in response to aggregating agents using light scattering detection method (Abstract). The instrument of Solen et al. is used in the clinical laboratory to evaluate the functional status of platelets in blood samples from patients suspected of abnormal platelet function (Abstract). The measurement is based on the scattering of light in the blood sample and does not require separation of erythrocytes from blood and therefore helps minimize the need for handling of blood by the laboratory personnel (Abstract). The instrument converts the light scattering data to provide the number and average size of the aggregates per unit volume at various times during the process of aggregation (Abstract).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to use the detection instrument of Solen et al. utilizing a light

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scattering measurement in the agglutination method of Favaloro et al. in view of Christophe et al. and Handin because the light scattering measurement instrument of Solen et al. does not require separation of erythrocytes from blood and therefore helps minimize the need for handling of blood by the laboratory personnel. Furthermore, the light scattering measurement instrument of Solen et al. provides quantitative analysis of platelet aggregation (agglutination) by measuring the number and average size of the aggregates per unit volume at various times during the process of aggregation.

25. Claim 61 is rejected under 35 U.S.C. 103(a) as being unpatentable over Favaloro et al. (*Pathology*, 1993, Vol. 25, pp152-158) in view of Christophe et al. (*Blood*, 1994, Vol. 83, pp3553-3561), Hoylaerts et al. (*Biochem. J.*, 1995, Vol. 386, pp453-463) and Handin (U.S. Patent No. 5,321,127, June 14, 1994) in light of Vicente (*J. Biol. Chem.*, 1988, Vol. 263, pp18473-18479).

Favaloro et al. in view of Christophe et al. , Hoylaerts et al., and Handin teaches a method for detecting vWD as discussed above. Handin further teaches that glyocalicin, which contains the majority of the extracellular portion of the GP1b(α) chain can be further digested to obtain an amino terminal 45 kDa fragment, which contain the vWF binding site (column 2, line-column 3, line 2). However, Favaloro et al. in view of Christophe et al., Hoylaerts et al., and Handin fails to teach a method, wherein the soluble form or a portion of GP1b(α) comprises amino acid residues His1-Val289 of GP1b(α).

Vicente teaches that 45 kDa fragment of GP1b(α) contains amino acid residues extending between His1-Arg293 of GP1b(α) (Abstract). Therefore one of ordinary skill in the art would readily realize that Handin's 45 kDa fragment of GP1b(α) would inherent include a portion of GP1b(α) comprising amino acid residues His1-Val289 of GP1b(α).

Response to Arguments

26. Applicant's arguments with respect to claims 31-41 and 48-59 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

27. No claim is allowed.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Unsu Jung whose telephone number is 571-272-8506. The examiner can normally be reached on M-F: 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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